

**ENVIRONMENTAL PROTECTION AGENCY**

**[EPA-HQ-OW-2009-0297; FRL-\_\_\_\_\_ - \_\_\_\_\_]**

**RIN 2040-AF08**

**Drinking Water: Perchlorate Supplemental Request for Comments**

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice.

---

**SUMMARY:** The Agency is seeking comments on additional approaches to analyzing data related to EPA's perchlorate regulatory determination. These additional comments are sought in an effort to ensure consideration of all the potential options for evaluating whether there is a meaningful opportunity for human health risk reduction of perchlorate through a national primary drinking water rule. EPA will make a final regulatory determination for perchlorate after considering comments and information provided in the 30-day comment period following this notice.

**DATES:** Comments must be received on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

**ADDRESSES:** Submit your comments, identified by Docket ID No. **EPA-HQ-OW-2009-0297**, by one of the following methods:

- [www.regulations.gov](http://www.regulations.gov): Follow the on-line instructions for submitting comments.
- Mail: Water Docket, Environmental Protection Agency, Mailcode: 2822T, 1200

Pennsylvania Ave., NW, Washington, DC 20460.

- Hand Delivery: Water Docket, EPA Docket Center (EPA/DC) EPA West, Room 3334, 1301 Constitution Ave., NW, Washington, DC. Such deliveries are only accepted during the Docket's normal hours of operation, and special arrangements should be made for deliveries of boxed information.

*Instructions:* Direct your comments to Docket ID No. **EPA-HQ-OW-2009-0297**. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at [www.regulations.gov](http://www.regulations.gov), including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through [www.regulations.gov](http://www.regulations.gov) or e-mail. The [www.regulations.gov](http://www.regulations.gov) website is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through [www.regulations.gov](http://www.regulations.gov) your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses. For additional instructions on submitting comments, go to Unit I.A of the **SUPPLEMENTARY INFORMATION** section of this

document.

*Docket:* All documents in the docket are listed in the [www.regulations.gov](http://www.regulations.gov) index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in [www.regulations.gov](http://www.regulations.gov) or in hard copy at the Water Docket, EPA/DC, EPA West, Room 3334, 1301 Constitution Ave., NW, Washington, DC. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the EPA Docket Center is (202) 566-2426.

**FOR FURTHER INFORMATION CONTACT:** Eric Burneson, Office of Ground Water and Drinking Water, Standards and Risk Management Division, at (202) 564-5250 or e-mail [burneson.eric@epa.gov](mailto:burneson.eric@epa.gov). For general information, contact the EPA Safe Drinking Water Hotline at (800) 426-4791 or e-mail: [hotline-sdwa@epa.gov](mailto:hotline-sdwa@epa.gov).

### **Abbreviations and Acronyms**

>—greater than

<—less than

BW— body weight

CBI— confidential business information

CDC— Centers for Disease Control and Prevention

DWI— drinking water intake

EPA— U.S. Environmental Protection Agency

FDA— U.S. Food and Drug Administration

FR— *Federal Register*

HA— Health Advisory

HRL— health reference level

IRIS— Integrated Risk Information System

kg— kilogram

L— liter

mg/kg— milligram per kilogram of body weight

mg/L— milligrams per liter (equivalent to parts per million [ppm])

MRL— Method Reporting Limit

NAS— National Academy of Science

NHANES— National Health and Nutrition Examination Survey

NOAEL— no observed adverse effect level

NOEL— no observed effect level

NRC— National Research Council

OW— Office of Water

PBPK— Physiologically-Based Pharmacokinetic

POD — point of departure

RAIU— Radioactive Iodide Uptake

RfD— reference dose

RSC— relative source contribution

SDWA— Safe Drinking Water Act

UCMR— Unregulated Contaminant Monitoring Regulation

µg— microgram (one-millionth of a gram)

US— United States

USDA— U.S. Department of Agriculture

## **SUPPLEMENTARY INFORMATION**

### **I. General Information**

#### *A. What Should I Consider as I Prepare My Comments for EPA?*

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide any technical information and/or data you used that support your views.
4. If you estimate potential burden or costs, explain how you arrived at your estimate.
5. Provide specific examples to illustrate your concerns.
6. Offer alternatives.
7. Make sure to submit your comments by the comment period deadline.
8. To ensure proper receipt by EPA, identify the appropriate docket identification number in the subject line on the first page of your response. It would also be helpful if you provided the name, date, and *Federal Register* (FR) citation related to your comments.

### **II. Background**

The statutory and regulatory background for this action is described in detail in the October 10, 2008, FR notice discussing EPA's initial regulatory determination for perchlorate (USEPA, 2008a). Briefly, the Safe Drinking Water Act (SDWA) section 1412, as amended in 1996, requires EPA to make a determination whether to regulate at least 5 contaminants from its contaminant candidate list (CCL) every 5 years. Once EPA determines to regulate a contaminant in drinking water, EPA must issue a proposed national primary drinking water regulation (NPDWR) and final NPDWR within certain set time frames. To regulate a contaminant in drinking water, EPA must determine that it meets three criteria: 1) the contaminant may have an adverse effect on human health, 2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern, and 3) regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems. To date, EPA has made final regulatory determinations for 20 contaminants from CCL1 and CCL2 and has not found that any of these contaminants meet all three criteria.

On October 10, 2008, EPA published a preliminary regulatory determination for perchlorate, requesting public comment on its determination that perchlorate did not meet the second and third criteria for regulation. The October 2008 notice describes in detail the bases for EPA's determination (USEPA, 2008a). EPA received extensive public comment on that notice.

Today, the Agency is seeking comments on additional approaches to analyzing data related to EPA's perchlorate regulatory determination. The EPA is requesting the additional comments in an effort to ensure that the Agency considers the potential options for evaluating whether there is a meaningful opportunity for human health risk reduction from perchlorate through a national primary drinking water rule. EPA's final decision may be a determination to

regulate. As discussed below, the additional alternatives under consideration could result in health reference levels which are much lower than the level identified in the October 2008 notice. The public comments EPA received pursuant to the October 10, 2008, notice of preliminary regulatory determination<sup>1</sup> and from the peer review of the supporting documents underscore the complexity of the scientific issues regarding the regulatory determination for perchlorate in drinking water.

EPA received 32,795 comment letters of which 31,632 (96%) letters were from seven different apparent mass mailing letter writing campaigns that did not support the preliminary determination. Of the remaining 1,163 comment letters that would be considered “unique,” 30 commenters provided EPA with detailed comments. Of those 30 comment letters, six supported EPA’s preliminary determination. These comments and other docket materials are available electronically at [www.regulations.gov](http://www.regulations.gov) (Docket ID No. EPA-HQ-OW-2008-0692).

In its October 2008 FRN, EPA referred to a draft report entitled “Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-Based Pharmacokinetic (PBPK) Modeling” (USEPA, 2008b). This draft report, which is described in Section III.A.1, was peer reviewed during the comment period on the regulatory determination. The external review draft (USEPA, 2008c) and a summary of significant comments made by the external peer reviewers and EPA’s responses (USEPA, 2008e) can be found at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=199347>. The peer review comments were complimentary and supportive of EPA’s modeling analysis and support document.

---

<sup>1</sup> On November 12, 2008, EPA extended the comment period for 15 days regarding EPA’s preliminary regulatory determination for perchlorate.

On January 8, 2009, EPA issued an interim health advisory (HA) to provide guidance to state and local officials in their efforts to address perchlorate contamination while EPA was reviewing scientific issues. A draft of the HA was peer reviewed by four external peer reviewers. The HA peer reviewers comments are discussed in Section III.A.2 of this notice. The Interim Health Advisory (USEPA. 2008d) can be found at <http://www.epa.gov/safewater/contaminants/unregulated/perchlorate.html> and the summary of significant comments made by the external peer reviewers (USEPA. 2008e) can be found at [http://www.epa.gov/ogwdw/contaminants/unregulated/pdfs/perchlorate\\_ha\\_comment\\_response.pdf](http://www.epa.gov/ogwdw/contaminants/unregulated/pdfs/perchlorate_ha_comment_response.pdf).

In January of this year, EPA announced that we planned to seek additional input from the National Research Council (NRC) on perchlorate. The NRC previously studied perchlorate health implications from March, 2003 until they issued their report in January, 2005 (NRC, 2005). EPA has compiled and evaluated additional scientific studies relevant to perchlorate health effects and exposure available since publication of the 2005 NRC report. As previously stated, EPA also has obtained peer review and public comment on the Agency's analysis of a number of these studies. The Agency believes that further review by the NRC would unnecessarily delay regulatory decision making for perchlorate. Therefore, EPA is not, at present, planning to request additional NRC review of issues related to perchlorate. Instead, EPA is issuing this notice and seeking comment on a broad range of alternative approaches to the interpretation of the scientific data relevant to a regulatory determination for perchlorate in drinking water. However, EPA requests comment upon whether further review by the NRC is warranted. EPA also notes that if the Agency were to make a final determination to regulate perchlorate, the Agency, in accordance with the SDWA, would seek review by the Science



Advisory Board prior to proposal of any maximum contaminant level goal and national primary drinking water rule.<sup>2</sup>

In issuing this supplemental notice, EPA is not making a final regulatory determination for perchlorate nor are we changing the Interim Health Advisory Level of 15 µg/L. EPA will consider comments on the information received on this notice, as well as those received on the October 10, 2008, FR notice, and those received on the peer review of supporting documents before completing its regulatory determination for perchlorate. EPA may also revise the Interim Health Advisory as part of this process.

### **III. Alternative Approaches to Analyzing Scientific Data Related to Perchlorate in Drinking Water**

EPA is requesting comment on key issues related to the regulatory determination for perchlorate in drinking water. EPA is now considering a broader range of alternatives for interpreting the available data on: the level of health concern, the frequency of occurrence of perchlorate in drinking water, and the opportunity for health risk reduction through a national primary drinking water standard. These alternative interpretations may impact the Agency's final regulatory determination for perchlorate. Therefore, EPA seeks comment on these issues and the alternative approaches the Agency is considering.

#### **A. *Interpretation of the Physiologically-Based Pharmacokinetic (PBPK) Modeling***

---

<sup>2</sup> The requirement for national drinking water regulations are in SDWA Section 1412. EPA's Web page describes the regulatory development process (see <http://www.epa.gov/safewater/standard/setting.html>). [SDWA section 1412.e](#) requires that EPA request comment from the Science Advisory Board prior to proposal of a maximum contaminant level goal and national primary drinking water regulation.

1. EPA's PBPK Modeling Analysis in the October 2008 FR Notice

The NRC (NRC, 2005) found that the inhibition of iodide uptake by the thyroid should be used as the basis for a perchlorate risk assessment. In the October, 2008, FR notice, EPA describes a Physiologically-Based Pharmacokinetic (PBPK) modeling analysis prepared by the Agency utilizing a series of papers (e.g., Clewell et al., 2007) discussing PBPK models that estimated the effect of perchlorate on iodide uptake for the pregnant woman and fetus, the lactating woman and neonate, and the young child. EPA used the PBPK modeling analysis to estimate the iodide uptake inhibition for these sensitive life stages consuming food containing perchlorate at mean levels, and drinking water containing perchlorate at an HRL of 15 µg/L at the 90<sup>th</sup> percentile consumption rate.

EPA found that the predicted radioactive iodide uptake (RAIU) inhibition for all subgroups was comparable to, or less than, the RAIU at the no observed effect level (NOEL) selected by the NRC. Based on this outcome, EPA concluded that by protecting the fetus of the hypothyroid or iodide-deficient woman from the effects of perchlorate on the thyroid, all other life stages and subgroups would be protected.

EPA requested comment on the model in the October 2008 FR notice in addition to conducting a peer review on the application of the model to non-adult life stages.

2. What Were the Key Scientific Issues Raised by Commenters

Many of the public comments EPA received on the PBPK model in response to the October 2008 FR notice objected to the Agency's use of a model that had not been peer reviewed. Concurrently with the public comment period, the PBPK model analysis underwent a rigorous peer review by eight experts. Response by the PB model analysis peer reviewers indicated that the modifications made to the model and the changes to physiological parameters were an improvement over the Clewell model, and all reviews were generally supportive of the analysis. Based on the external peer review comments, the models and the report entitled, "Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-Based Pharmacokinetic (PBPK) Modeling" were revised.

As previously discussed, comments were also received from four peer reviewers for the Interim Drinking Water Health Advisory (HA) on the application of the model in identifying sensitive life stages. One HA peer reviewer noted that the use of the PBPK model did "provide an estimate of perchlorate exposure to average weight babies of healthy breastfeeding women." However, this HA peer reviewer continued on to recommend that the exposure estimate be expanded to include consideration of small birth weight and preterm infants.

Another peer reviewer recommended that the uncertainty inherent in the modeling exercise should be made more transparent to the public. This uncertainty was linked to the modeling code, the availability of data for the many variable parameters in the model, the combination and handling of the data selected for use in simulations, and, in particular, the lack of human data for specific life stages including pregnant women and their fetuses, lactating women and their babies, and bottle-fed infants for which rat data were adapted. The inability of the model to reflect iodide nutritional status also was cited by three peer reviewers as an important limitation.

Individual peer reviewers raised two additional concerns: 1) that the use of animal data to predict human responses appears to run counter to the NRC finding that animal data cannot be used to quantitatively predict the response of humans due to species differences, and 2) that EPA appeared to use the PBPK model to modify the reference dose (RfD) for infants, justifying the allowance of exposures that clearly exceeded the RfD established by the NRC.

Peer reviewers further noted that the PBPK model and the EPA assessment did not account for the activity of other compounds with similar actions on the thyroid. This issue was also raised by EPA's Office of Inspector General (OIG) in reference to EPA's perchlorate risk assessment (See section III.C.2 for more information). One reviewer stated that the application of the PBPK model by the Agency as cited in the Interim Health Advisory implied an inappropriate certainty in the results that was not warranted. This reviewer recommended confining the use of the PBPK model to exploring the impact of varying physiological parameters and exposure data among life stages.

### 3. Alternative Approaches EPA is Also Now Considering

Based on the comments received on the application of the PBPK model as described in the October 2008 notice and the Interim HA, EPA is re-evaluating how best to incorporate the PBPK modeling analysis into its evaluation of perchlorate, if at all.

One approach might be to use the PBPK modeling analysis to explore the relative sensitivity of the various life stages of concern to a fixed dose such as the point of departure (POD) or the reference dose (RfD). For example, EPA has examined the effect of a dose equal to the POD on RAIU for a number of different life stages. The POD for the perchlorate risk

assessment (7 µg/kg/day) was recommended by the NRC. The POD is the lowest dose administered in the Greer et al. (2002) clinical study, and resulted in a “very small decrease (1.8%) in radioiodide uptake ... well within the variation of repeated measurements of normal subjects (NRC, 2005).” The POD used was determined by NRC to be a No Observed Effect Level (NOEL). The NRC stated that use of a NOEL differs from the traditional approach to deriving an RfD, which bases the critical effect on an adverse outcome, and that using a nonadverse effect that is upstream of the adverse effect is a more conservative and health-protective approach to perchlorate hazard assessment. The NRC also recommended that EPA derive an RfD by applying a 10 fold uncertainty factor to the POD to account for differences between healthy adults and the most sensitive population, fetuses of pregnant women who might have hypothyroidism or iodide deficiency. When compared to the average adult, the 7-day old breast-fed infant and the fetus of the pregnant woman at gestation week 40 were identified by EPA’s analysis as the most sensitive subgroup with respect to percent RAIU inhibition at a dose to the lactating or pregnant women equal to the POD. (See Table 1 for the model-predicted RAIU inhibition and relative sensitivity at the POD of different subgroups compared to the average adult, based on EPA’s modified PBPK model.)

The predicted percent RAIU inhibition is approximately 7.8-fold higher for the 7-day old breast-fed infant and 6.7- fold higher for the fetus (at gestational week 40) than for the average adult. (Simulations at earlier gestation weeks indicate that the fetus is more sensitive than the adult throughout pregnancy, but data available for validation of these parameters are minimal and are considered too quantitatively uncertain to assign exact relative sensitivities.) The same analysis shows that the predicted percent RAIU inhibition is approximately one and a half fold higher for the bottle-fed infant (7-60 days) compared to the average adult, and is approximately

equal for the 1-2 year old child and the average adult. However, the drinking water exposure data discussed in section III.B.3 show that infants less than six months in age generally consume five to eight times more water than pregnant women or women of child bearing age on a per body weight basis, and so will receive a higher dose for any given drinking water concentration.

Table 1. Model-predicted radioactive iodide uptake (RAIU) inhibition and relative sensitivity of different subgroups compared to the average adult at a dose equal to the point-of-departure (POD) based on the EPA's modified PBPK models.

Population or Life Stage	Body weight (kg)	Dose <sup>i</sup> (µg/kg-d)	RAIU inhibition	Relative sensitivity vs. average adult
Average Adult <sup>a</sup>	70	7	1.6%	1
Woman (child-bearing age)	68	7	3.0% <sup>b</sup>	1.8
Pregnant woman and Fetus (Gestation Week 40)	Mom: 79	7	6.1% <sup>c</sup>	3.7
	Fetus: 3.5	--	11% <sup>c</sup>	6.7
Lactating woman and Breast-fed infant (7 d)	Mom: 74	7	2.1% <sup>d</sup>	1.3
	Infant: 3.6	Mom = 7	12.5% <sup>d, e</sup>	7.8
		Infant = 7 (Mom = 2.7)	5.4% <sup>d, e, f</sup>	3.3
Lactating woman and Breast-fed infant (30 d)	Mom: 73	7	2.0% <sup>d</sup>	1.2
	Infant: 4.2	Mom = 7	9.8% <sup>d, e</sup>	6.1
		Infant = 7 (Mom = 3.0)	4.4% <sup>d, e, f</sup>	2.7
Lactating woman and Breast-fed infant (60 d)	Mom: 72	7	2.0% <sup>d</sup>	1.2
	Infant: 5.0	Mom = 7	7.9% <sup>d, e</sup>	4.9
		Infant = 7 (Mom = 3.6)	4.2% <sup>d, e, f</sup>	2.7
Bottle-fed infant (60 d)	Infant: 5.0	7	2.5% <sup>e</sup>	1.5
Child (0.97 yr) <sup>g</sup>	Child: 10	7	1.7% <sup>h</sup>	1.1
Child (2 yr)	Child: 14	7	1.7% <sup>h</sup>	1.1

<sup>a</sup> The body weight (70 kg) for the average adult is the default weight used by EPA for past regulatory determinations. All other body weights are generated by the model.

<sup>b</sup> Maternal body weight was held at the value defined at the start of pregnancy (BW = 67.77 kg), and the 'average adult' urinary clearance values as published by Merrill et al. (2005) were used.

- <sup>c</sup> Results are based on using the maternal urinary clearance as published in Clewell et al. (2007), which equal about half of the average adult clearance.
- <sup>d</sup> Results are based on setting the maternal clearance rates of both perchlorate and iodide during lactation equal to that of the average adult. Clewell et al. (2007) used an iodide clearance rate equal to that of an average adult, but a perchlorate rate only half that of the average adult.
- <sup>e</sup> %RAIU inhibition given for the infant is provided based upon a value of urinary clearance scaled from the adult by  $BW^{2/3}$  to approximate surface-area scaling, and then multiplied by a rising fraction vs. age based on data (DeWoskin and Thompson, 2008) to reflect the reduction in glomerular filtration rates. Clewell et al. (2007) scaled urinary clearance by  $BW^{0.75}$ , rather than adjusting based on GFR.
- <sup>f</sup> These %RAIU inhibition values are based on an internal dose to the breast-fed infant of 7  $\mu\text{g}/\text{kg}\cdot\text{day}$ , the same as for the other subgroups. Maternal dose rates lower than the POD are needed to provide 7  $\mu\text{g}/\text{kg}\cdot\text{day}$  to the infant as shown in the table. These doses differ due to changes in body weights and other PK factors with age.
- <sup>g</sup> Because EPA typically uses a 10 kg child as a default assumption for its drinking water health advisories, the model was run for a child at 0.97 yr, the age at which the model-simulated body weight for a child is 10 kg.
- <sup>h</sup> Results were obtained by setting urinary clearance constants for the older child equal to the average adult (Merrill et al., 2005) and scaling by  $BW^1$ .
- <sup>i</sup> The dose equal to the POD is 7  $\mu\text{g}/\text{kg}\cdot\text{day}$  which is 10 fold greater than the RfD. The predicted RAIU inhibition at the RfD would be less than those shown in Table 1.

The modeling analysis may be used as a tool to predict the impact of different perchlorate drinking water concentrations on RAIU across life stages. Understanding the potential impact of reducing perchlorate concentrations may be especially important for considering bottle-fed infants for whom a major portion of the diet may consist of water used to rehydrate formula.

Another approach EPA is also considering would be to not use the PBPK modeling analysis to inform the selection of the HRL for its regulatory determination but instead apply the RfD directly to the exposures of other sensitive life stages to develop separate HRLs for these life stages as described in Section III.B.

#### 4. Request for Comment on Alternative Approaches

EPA seeks comments on the following issues:

- a. EPA requests comment on using the PBPK model to evaluate the relative sensitivity of the various life stages to perchlorate exposure in drinking water.
- b. EPA requests comment on the utility of the PBPK model for predicting the impact of different perchlorate drinking water concentrations on sensitive life stages to inform HRL selection.
- c. EPA requests suggestions for ways to use the PBPK modeling analysis to inform the regulatory determination for perchlorate that are different from those described in this notice or the October 10, 2008, notice.

B. *Alternative HRLs Based Upon Body Weight and Water Consumption of Other Life Stages*

1. Analysis and Interpretations from the October 2008 FR Notice

In our October 2008 FR notice, EPA requested comments on an HRL of 15 µg/L to protect pregnant women and their fetuses based upon the Agency's RfD, recommended by the NRC, and the following exposure estimates:

$$\text{HRL} = \text{RfD} \times \text{BW/DWI} \times \text{RSC}$$

Where:

RfD = Reference dose (0.7 µg/kg/day)

BW = Body weight (70 kg, default value)



DWI = Drinking water intake (2 L/day, default value)

RSC = Relative source contribution (62% for pregnant women)

In calculating the HRL of 15 µg/L, EPA used adult default values for both body weight (the mean body weight for men and women, 70 kg) and drinking water intake (84<sup>th</sup> percentile, 2 L/day). The RSC is the percentage of the reference dose remaining for drinking water after other sources of exposure to perchlorate have been considered (e.g., food). EPA used the pregnant women's estimated 90<sup>th</sup> percentile perchlorate intake from food to determine the RSC of 62%. In past regulatory determinations on most other noncarcinogenic contaminants, EPA has used an RSC default value of 20% for screening purposes to estimate the HRL when it has lacked adequate data to develop empirical RSCs for those contaminants (for sulfate and sodium EPA did not use an RSC to determine the HRL). For the October 2008 notice, the Agency believed that sufficient exposure data were available for perchlorate to enable EPA to estimate a better informed RSC and HRL that is more appropriate for fetuses of pregnant women (the most sensitive life stage identified by the NRC). These exposure data include the further analysis by EPA of the Unregulated Contaminant Monitoring Regulation (UCMR) data and the Centers for Disease Control and Prevention's (CDC's) National Health and Nutrition Examination Survey (NHANES) biomonitoring data, as well as the Food and Drug Administration's (FDA's) Total Diet Study (TDS) (73 FR 60269-72, October 10, 2008). The EPA analysis provided a distribution of exposure (not just a mean) specific to almost 100 pregnant women who are not likely to have been exposed to perchlorate from their drinking water, although it did not separate out iodine-deficient pregnant women because of data limitations. EPA estimated that for 90% of the pregnant women, exposure to perchlorate from food is equal to, or less than, 0.263 µg/kg/day

(90<sup>th</sup> percentile). This represents nearly 38% of the RfD, leaving an RSC for water of 62%.

## 2. What Were the Key Issues Raised by Public Commenters?

The comments EPA received underscore the complexity of the scientific issues and many were critical of EPA's derivation of the HRL. Of those that provided detailed comments, many were concerned about the adequacy of the HRL to address all sensitive life stages (e.g., pre-term and full-term infants). For example, a number of commenters argued that the proposed HRL is too high for infants because an HRL of 15 µg/L would allow daily exposures that are two to five times higher than the RfD.

One commenter cites a March 8, 2006, letter from the Children's Health Protection Advisory Committee to the EPA Administrator. The commenter states, "... [T]he committee emphasized the higher exposure of infants to perchlorate and greater susceptibility to serious negative effects associated with perchlorate exposure. Neither of these issues, however, was given adequate consideration in the Preliminary Determination."

Another commenter addresses EPA's use of default values in deriving the HRL stating, "... EPA continues to use the obsolete default of 70 kg for body weight and 2 L/day of water consumption when these values certainly do not apply to pregnant women. These defaults are specifically intended for the population in general, and should be superseded by more specific and appropriate values when risk assessment is being conducted for a defined subpopulation (U.S. EPA, 2004, 2005)."

## 3. Alternative Approaches for Calculating HRLs

EPA agrees that reassessing exposure assumptions and other life stages warrants further consideration. The NRC (2005) identified “the fetuses of pregnant women who might have hypothyroidism or iodide deficiency” as “the most sensitive population,” but also identified infants and developing children as additional “sensitive populations.” Infants and young children have greater exposure to contaminants in food and water because of greater consumption of food and water on a per unit body weight basis. Therefore, these life stages may be the most vulnerable populations when their relative exposure is considered. Therefore, EPA is considering alternative approaches to deriving HRLs by evaluating exposures at different life stages. EPA is considering alternative HRLs that are estimates of the maximum concentration of perchlorate that can be consumed in drinking water without an individual’s total perchlorate dose from food and water exceeding the RfD. EPA’s Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants (USEPA, 2005) recommends the following 10 age groups be considered in exposure assessments for children.

- Less than 12 Months old: birth to < 1 month, 1 to < 3 months, 3 to < 6 months and 6 to < 12 months.
- Greater than 12 months old: 1 to < 2 years, 2 to < 3 years, 3 to < 6 years, 6 to < 11 years, 11 to < 16 years, and 16 to < 21 years.

EPA’s Guidance for Risk Characterization (USEPA, 1995) recommends that when considering exposure to use both high end (i.e., 90<sup>th</sup> and 95<sup>th</sup> percentile) and central tendency (average or median estimates) descriptors to convey the variability in risk levels experienced by different individuals in the population.

Table 2 arrays the alternative HRLs at the average 90<sup>th</sup> and 95<sup>th</sup> percentile drinking water ingestion rates for each of the 10 childhood life stages (as well as for pregnant women and women of child-bearing age, 15 to 44). The table uses the life stage specific drinking water intake data that are adjusted to account for the body weight of the individual. EPA's Child-Specific Exposure Factors Handbook (USEPA, 2008f) recommends values for drinking water ingestion rates for each of recommended children's life stage based on a study of drinking water ingestion of the U.S. population by Kahn and Stralka (2008). The study reports ingestion estimates for "all individuals" and for "consumers only." Estimates reported for "all individuals" include all survey participants regardless of whether they consumed water during the 2-day survey period. Ingestion estimates for "consumers only" are generated from only the respondents who reported ingestion of drinking water from a community water system during the survey period. The authors report that this group is often the primary focus in analyses of risk due to ingestion of water that may be contaminated. Consequently, this is the only group presented in Table 2.

In addition to identifying infants and developing children as sensitive life stages, as noted previously, the NAS identified the fetuses of iodide deficient pregnant women as the most sensitive population (or life stage). To address concerns that the default weight and ingestion rates provided in the October 2008 notice do not apply to this group, EPA has included an alternative HRL for this life stage in Table 2. This value is calculated based on body weight and drinking water ingestion information specifically from pregnant women (USEPA, 2004).

EPA notes that for six life stages in Table 2 (birth to < 1 month, 1 to < 3 months, 3 to < 6 months, 16 to 18 years and 18 to 21 years and for pregnant women), the sample size used to estimate some of the drinking water ingestion rates (denoted in Table 2 by foot note <sup>c</sup>) do not

meet the minimum data requirements as described in the “Third Report on Nutrition Monitoring in the United States” (LSRO, 1995). However, these are the best available data to characterize drinking water ingestion for these specific life stages. EPA also notes that these data clearly show the trend that drinking water mean ingestion rate on a per body weight basis increases as the life stage age decreases. To address this potential concern regarding sample size for some of these drinking water ingestion rates, EPA also aggregated the three youngest recommended age groups into one category on Table 2 (birth to < 6 months) based on data from EPA (USEPA, 2004). To address women of childbearing age, EPA presents HRLs calculated based upon drinking water ingestion data for women ages 15 to 44.

To estimate dietary exposure to perchlorate and to calculate RSCs, EPA used data available from two studies previously described by EPA, the FDA’s Total Diet Study (Murray et al., 2008) and the NHANES-UCMR Analysis (73 FR 60269-73, October 10, 2008). In cases where these studies did not provide a dietary exposure estimate for one of the recommended child-specific life stages/age groups, EPA applied the RSC calculated for the age group closest to the age group of interest. This meant that the RSCs for the age groups between birth and 6 months, 59%, were based on the mean dietary exposure estimate for infants ages 6 through 11 months, 0.29 µg/kg-day, derived from FDA’s Total Diet Study. We understand that infant diets vary significantly between birth and age 11 months and that the TDS mean dietary perchlorate exposure estimates for ages 6 through 11 months consider consumption of baby foods that are not consumed by younger infants (see

[www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/Perchlorate/ucm077615.htm](http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/Perchlorate/ucm077615.htm)). Researchers from the CDC (Schier et al., 2009) recently published a study in which they estimated exposures to perchlorate from the consumption of infant formula. For

infants age 1 month, the researchers' central tendency estimate of perchlorate daily dose from consumption of bovine milk-based infant formula with lactose (the type of formula with the highest concentrations of perchlorate) was also 0.29 µg/kg-day, corresponding to an RSC of 59%. Thus, EPA's RSC for young infants, 59%, is supported through two different estimates of central tendency infant dietary perchlorate exposure.

**Table 2. Alternative HRLs at the Average, 90<sup>th</sup> and 95<sup>th</sup> Percentile Drinking Water Ingestion Rates for Various Life Stages.**

Life Stage	RfD (µg/Kg-day)	RSC <sup>a</sup>	Mean Ingestion Rate <sup>d</sup> (mL/Kg-day) <sup>b</sup>	Alt HRL (µg/L)	90 <sup>th</sup> Percentile Ingestion Rate <sup>d</sup> (mL/Kg-day) <sup>b</sup>	Alt HRL (µg/L)	95 <sup>th</sup> Percentile Ingestion Rate <sup>d</sup> (mL/Kg-day) <sup>b</sup>	Alt HRL (µg/L)
Birth to < 1 month	0.7	59%	137	3	235 <sup>c</sup>	2	238 <sup>c</sup>	2
1 to < 3 months	0.7	59%	119	3	228 <sup>c</sup>	2	285 <sup>c</sup>	1
3 to < 6 months	0.7	59%	80	5	148	3	173 <sup>c</sup>	2
Birth to < 6 months	0.7	59%	95	4	184	2	221	2
6 to < 12 months	0.7	59%	53	8	112	4	129	3
1 to < 2 years	0.7	44%	27	11	56	6	75	4
2 to < 3 years	0.7	44%	26	12	52	6	62	5
3 to < 6 years	0.7	60%	24	18	49	9	65	6
6 to < 11 years	0.7	71%	17	29	35	14	45	11
11 to < 16 years	0.7	84%	13	45	26	23	34	17
16 to < 18 years	0.7	80%	12	47	24	23	32 <sup>c</sup>	18
18 to < 21 years	0.7	80%	13	43	29	19	35 <sup>c</sup>	16
Pregnant Women <sup>c</sup>	0.7	62% <sup>c</sup>	14 <sup>c</sup>	31	33 <sup>c</sup>	13	43 <sup>c</sup>	10
Women Ages 15-44	0.7	80%	15	37	32	18	39	14

<sup>a</sup> RSC calculated for nearest age range based on the mean dietary intake from TDS (see Table 5 at 73 FR 60275, October 10, 2008), RSC for pregnant women and women ages 15-44 based on the 90<sup>th</sup> percentile dietary intake from NHANES-UCMR analysis (see Table 6 at 73 FR 60276, October 10, 2008).

<sup>b</sup> Drinking Water Ingestion Rates for consumers only in Community Water Systems taken from EPA's "Child-Specific Exposure Factors Handbook" (USEPA, 2008e). Except for values for infants from birth to 6 months, which are taken from Tables 5.2.A2 of EPA's "Estimated Per Capita Water Ingestion and Body Weight in the United States - An Update" (USEPA, 2004), and for Pregnant Women and Women Ages 15-44 which are taken from Table 6.2.A2 of EPA's "Estimated Per Capita Water Ingestion and Body Weight in the United States - An Update" (USEPA, 2004).

<sup>c</sup> The sample sizes for the estimates of ingestion rates for these life stages do not meet the minimum data requirements as described in the "Third Report on Nutrition Monitoring in the United States" (LSRO, 1995).

<sup>d</sup> Ingestion rate is adjusted for the self reported body weights from the CFSII.

<sup>e</sup> The most sensitive population identified by the NRC are the fetuses of pregnant women who might have hypothyroidism or iodide deficiency.

#### 4. Request for Comments

EPA seeks comments on the following issues:

- a. EPA requests comment on whether the alternative HRLs described in this notice appropriately take into account specific and appropriate exposure values for all potentially sensitive life stages, including infants, children and the fetuses of pregnant women (rather than the 70 kg body weight and 2 liter per day consumption used for past regulatory determinations).
- b. EPA requests comment on the alternative HRLs in Table 2 and which of these values would be appropriate levels of health concern against which to compare the levels of perchlorate found in public water systems.
- c. EPA requests comment on whether EPA used the best available and most appropriate data to estimate alternative HRLs in Table 2. EPA specifically requests comment on the drinking water ingestion rates in Table 2 (denoted by footnote <sup>c</sup>) where the sample size does not meet the minimum data requirements as described in the “Third Report on Nutrition Monitoring in the United States” (LSRO, 1995). Does aggregating life stages (birth to 6 months, and women ages 15- 44) address sample size limitation and still provide an accurate representation of the exposure to the most vulnerable life stages?
- d. EPA requests comment on the merits of the approach described here of deriving HRLs for sensitive life stages based on the RfD combined with the life stage specific exposure data and whether there are other approaches that may be useful for deriving HRLs.

### C. Occurrence Analysis

#### 1. Occurrence Analysis in the October 2008 *Federal Register* Notice

In the October 2008 FR notice, EPA presented information on the drinking water occurrence of perchlorate. The data source was EPA's UCMR 1 and the samples were collected between 2001 and 2005. A total of 34,331 samples were collected from 3,865 public water systems. EPA found that 1.9% of the samples (637 out of 34,331) had perchlorate at, or above, the minimum reporting level (MRL = 4 µg/L) and that 4.1% of the systems (160 out of 3,865 systems) reported perchlorate at, or above, the MRL in at least one sample. The average perchlorate concentration among systems that detected perchlorate was 9.85 µg/L and the median was 6.40 µg/L.

Table 3 presents EPA's estimates of the population served by water systems for which the highest reported perchlorate concentration was greater than various threshold concentrations ranging from 4 µg/L (MRL) to 25 µg/L. The fourth column presents a high end estimate of the population served drinking water above a threshold. This column presents the total population served by those drinking water systems in which at least one sample was found to contain perchlorate above the threshold concentration. EPA considers this a high-end estimate because it is based upon the assumption that the entire system population is served water from the entry point that had the highest reported perchlorate concentration. In fact, many water systems have



multiple entry points into which treated water is pumped for distribution to their consumers. For the systems with multiple entry points, it is unlikely that the entire service population receives water from the one entry point with the highest single concentration. Therefore, EPA also is providing a less conservative estimate of the population served water above a threshold in the fifth column in Table 3. EPA developed this estimate by assuming the population was equally distributed among all entry points. For example, if a system with 10 entry points serving 200,000 people had a sample from a single entry point with a concentration at or above a given threshold, EPA assumed that the entry point served one-tenth of the system population, and added 20,000 people to the total when estimating the population in the last column of Table 3. This approach may provide either an overestimate or an underestimate of the population served by the affected entry point. In contrast, in the example above, EPA added the entire system population of 200,000 to the more conservative population served estimate in column 4, which is most likely an overestimate. EPA noted that the population estimates in Table 3 are for people at all life stages and estimated that at any one time, 1.4 percent of the population in Table 3 are pregnant women based upon data from the U.S. Census Bureau.

<b>Table 3. UCMR 1 Occurrence and Population Estimates for Perchlorate Above Various Thresholds</b>				
Thresholds <sup>a</sup>	PWSs with at Least 1 Detection > Threshold of Interest	PWS Entry or Sample Points with at Least 1 Detection > Threshold of Interest <sup>b</sup>	Population Served by PWSs with at Least 1 Detection > Threshold of Interest <sup>c</sup>	Population Estimate for Entry or Sample Points Having at Least 1 Detection > Threshold of Interest <sup>d</sup>
4 µg/L	4.01% (155 of 3,865)	2.48% (371 of 14,987)	16.6 M <sup>e</sup>	5.1 M
5 µg/L	3.16 % (122 of 3,865)	1.88 % (281 of 14,987)	14.6 M	4.0 M
7 µg/L	2.12 % (82 of 3,865)	1.14 % (171 of 14,987)	7.2 M	2.2 M

10 µg/L	1.35 % (52 of 3,865)	0.65 % (97 of 14,987)	5.0 M	1.5 M
12 µg/L	1.09 % (42 of 3,865)	0.42 % (63 of 14,984)	3.6 M	1.2 M
15 µg/L	0.80 % (31 of 3,865)	0.29 % (44 of 14,987)	2.0 M	0.9 M
17 µg/L	0.70 % (27 of 3,865)	0.24 % (36 of 14,987)	1.9 M	0.8 M
20 µg/L	0.49 % (19 of 3,865)	0.16 % (24 of 14,987)	1.5 M	0.7 M
25µg/L	0.36 % (14 of 3,865)	0.12 % (18 of 14,987)	1.0 M	0.4 M
Footnotes: <sup>a</sup> All occurrence measures in this table were conducted on a basis reflecting values greater than the listed thresholds. <sup>b</sup> The entry/sample-point-level population served estimate is based on the system entry/sample points that had at least 1 analytical detection for perchlorate greater than the threshold of interest. The UCMR 1 small system survey was designed to be representative of the nation's small systems, not necessarily to be representative of small system entry points. <sup>c</sup> The system-level population served estimate is based on the systems that had at least 1 analytical detection for perchlorate greater than the threshold of interest. <sup>d</sup> Because the population served by each entry/sample point is not known, EPA assumed that the total population served by a particular system is equally distributed across all entry/sample points. To derive the entry/sample point-level population estimate, EPA summed the population values for the entry/sample points that had at least 1 analytical detection greater than the threshold of interest. <sup>e</sup> This value does not include the population associated with 5 systems serving 200,000 people that measured perchlorate at 4 µg/L in at least one sample because the table only shows population estimates greater than each of the thresholds in the first column.				

The Agency also evaluated supplemental drinking water monitoring data for perchlorate in California and Massachusetts. EPA believes these States' monitoring results are generally consistent with the results collected by EPA under UCMR 1. Perchlorate occurrence analysis from California and Massachusetts can be found online at:

[www2.cdph.ca.gov/certlic/drinkingwater/Pages/Perchlorate.aspx](http://www2.cdph.ca.gov/certlic/drinkingwater/Pages/Perchlorate.aspx) and [www.mass.gov/dep/water/drinking/percinfo.htm#](http://www.mass.gov/dep/water/drinking/percinfo.htm#) sites respectively.

## 2. What Were the Key Issues Raised by Commenters?

EPA received comments on the proposed decision not to regulate perchlorate based on the population exposed above the HRL. Some comments objected to the Agency's proposed HRL as being "inappropriately high" thereby "greatly reducing the size of the population predicted to be exposed at a level of public health concern . . . and significantly minimizing the need for regulation of perchlorate from an occurrence standpoint."

One commenter believes that, "Approximately 4% of public water supplies serving 17 million Americans would be in exceedance of an HRL between 2 and 6 µg/L. This is 15 million more at risk individuals than currently estimated by the Agency."

Another commenter believes that at an HRL of 2 µg/L, 16.6 million would be exposed, and another commenter states that if EPA set the HRL at 5 µg/L, then 5 – 7 times more individuals would be exposed above the HRL than at 15 µg/L.

However, one commenter points out that, "An MCL of 2 µg/L could impact approximately 4% of public water systems nationally. At this level, regional impacts in California and Texas would be greater due to the higher geographical concentration of detections in those states. Yet it should be noted that water systems in Massachusetts, New Jersey and California have already established regulatory limits of 2 µg/L, 5 µg/L and 6 µg/L respectively, thereby capping the population exposure potential from community drinking water sources in those states."

### 3. Numbers of Systems and Populations that Would be Exposed at Levels Exceeding the Alternative Approaches the Agency is Considering

EPA plans to use the UCMR 1 perchlorate data to conduct analyses to estimate the number of systems and populations-served by systems that would be exposed to the various alternative HRL concentrations of perchlorate. Estimates will be made of the populations-served by systems for which the highest reported perchlorate concentration exceeds the various threshold concentrations ranging from 1 µg/L to 25 µg/L. One limitation to the UCMR 1 data is that the perchlorate analytical method MRL is 4 µg/L; only perchlorate sample detections greater than or equal to 4 µg/L can be dependably quantified and reported. Any perchlorate sample concentration with a value between 0 and 4 µg/L is recorded in the UCMR 1 data as a “non-detection.” Therefore, to estimate perchlorate occurrence relative to concentrations both above and below the MRL of 4 µg/L, while fully using all perchlorate detection and non-detection data, it is necessary to estimate occurrence using modeling techniques

EPA is considering using a Bayesian hierarchical model (a form of probabilistic model that uses maximum likelihood estimation techniques) to estimate perchlorate occurrence and to estimate the uncertainty and variability of those occurrence estimates. For this modeling effort, EPA could use the basic assumption that the national distribution of perchlorate sample concentrations can be modeled as a lognormal distribution. The lognormal distribution is a fundamental probability distribution that is used commonly and effectively to characterize environmental contaminant occurrence. The basic characteristic of a lognormal distribution is that the logarithms of the values being evaluated (in this case, the perchlorate concentrations of UCMR 1 samples of drinking water) are normally distributed. One property of the lognormal distribution that makes it particularly well-suited to describing phenomena like environmental contaminant occurrence data is that it is bounded by zero on the low end and it reflects a “right-

skewed” distribution—that is, it has a tail in the upper end—that is consistent with having a small proportion with relatively high values.

The Bayesian model could estimate the number of public water systems, and populations-served by systems, with at least one estimated sample detection greater than 1, 2, 3, 4, 5, 7, 10, 12, 15, 17, 20, and 25 µg/L. EPA notes that systems or entry/sample points with at least one detect above the threshold may not expose the population to this level at all times. At any particular time, perchlorate levels may be lower or higher than the highest estimated sample detection. However, EPA believes this approach more closely reflects the short term exposure during life stages of concern (i.e., fetuses, pre-term newborns, infants and young children) than does the estimated mean concentration of perchlorate at a system. EPA underscores the fact that the estimated total population exposed at thresholds that lie below the perchlorate MRL of 4 µg/L would be equal to, if not greater than, the corresponding high end estimate of 16.8 million people. To estimate the portion of the total population that is at a childhood life stage potentially exposed at these thresholds, EPA could use U.S. Census data as it did in the October 2008 FR notice to estimate the number of pregnant women potentially exposed above the HRL and could also estimate the number of infants and children potentially exposed above the HRL.

Perchlorate monitoring data from the State of Massachusetts could be used to help characterize the distribution of very low perchlorate concentration occurrence. Massachusetts monitoring uses a modified version of the EPA laboratory analytical method for perchlorate that has a MRL of 1 µg/L. This is the only known, state-wide monitoring program that uses an analytical method with an MRL lower than 4 µg/L. Bayesian hierarchical modeling can use the Massachusetts data to improve the model estimates in the lower concentration ranges.

#### 4. Request for Comment on Alternative Approaches

EPA seeks comments on the following issues:

- a. EPA requests comment on the potential use of a Bayesian model to estimate the number of public water systems, and populations-served by such systems, with at least one estimated sample detection greater than 1, 2, 3, 4, 5, 7, 10, 12, 15, 17, 20, and 25 µg/L.
- b. EPA requests comment on using U.S. Census data to estimate the portions of the population that are in the sensitive life stage at any one time.
- c. EPA requests comment on how the Agency should account for the variation of perchlorate levels over time in public water systems. EPA believes that estimating the number of systems, entry points and populations with at least one detection above the HRL is appropriate for the perchlorate regulatory determination because a single quarterly or semi-annual sample more closely reflects the short term exposure during life stages of concern (i.e., fetuses, pre-term newborns, infants and young children). However, EPA requests comment on whether the Agency should consider other approaches such as estimating the number of systems, entry points and populations with two or more detections above HRL or some other approach.

#### **IV. Consideration of Studies Published Since EPA Adopted the NAS RfD for Perchlorate**

EPA's preliminary regulatory determination is based on NRC's (NRC, 2005) recommendation to use data from the Greer et al. (2002) study as the basis for the perchlorate RfD/risk assessment.

Since the publication of the NRC report, researchers have investigated perchlorate occurrence in humans by analyzing for perchlorate in urine and breast milk—such biomonitoring data has the potential to better inform EPA's analysis of exposure to perchlorate through food and water and to provide insight into the possible interactions of other physiologic conditions (e.g., iodine deficiency) with perchlorate ingestion. EPA's preliminary regulatory determination described the consideration of these studies, many of which were published after the NRC report (including, but not limited to, Blount et al. (2006 and 2007), Steinmaus et al. (2007), and Amitai et al. (2007)) (73 FR 60267-68, October 10, 2008).

CDC researchers published two biomonitoring papers using CDC's 2001-2002 NHANES data – the first study measured perchlorate in urine (Blount et al., 2006) and the second examined the relationship between urinary perchlorate and thyroid hormone levels (Blount et al., 2007). In the urinary biomonitoring study, the authors found perchlorate in all samples tested (2,820 survey participants ages six and older) and estimated a total daily perchlorate dose for adults (doses for children were not calculated). The median dose was about one tenth (0.066 µg/kg/day) of the RfD, while the 95<sup>th</sup> percentile dose was about one third of the RfD (0.234 µg/kg/day). In the second study, which examined the relationship between urinary levels of perchlorate and blood serum levels of thyroid hormones, Blount et al. (2007) found that for women with low iodine levels (urinary iodide levels less than 100 µg/L) urinary perchlorate is associated with a decrease in (a negative predictor for) T4 levels and an increase in (a positive predictor for) thyroid stimulating hormone levels. The perchlorate exposures at which this

association was observed are lower than anticipated based on other studies. The study authors indicated that further research needs to be performed to confirm these findings. The subsequent Steinmaus (2007) analysis of the same NHANES 2001-2002 epidemiological data concluded that thiocyanate in tobacco smoke and perchlorate interact in affecting the thyroid function in low-iodine women. The Amitai et al. study assessed thyroid hormone (thyroxine) values in newborns in different perchlorate exposure groups (low, high and very high) and found no significant differences.

In studies analyzing breast milk for perchlorate, Pearce et al. (2007) and Kirk et al. (2005, 2007) all found perchlorate in study samples. The objective of the Pearce et al. (2007) study was “to determine whether breast milk iodine concentrations in Boston-area women are adequate for infant nutrition, and whether breast milk iodine concentrations may be associated with environmental perchlorate or cigarette smoke exposure.” Pearce et al. (2007) did not find a significant correlation with either breast milk perchlorate or urinary perchlorate levels with breast milk iodine concentrations. The objective of the Kirk et al. (2005) study was to determine the amount of perchlorate to which children are exposed by measuring perchlorate and iodide levels in cow and human breast milk and then comparing these numbers to corresponding levels of perchlorate in drinking water in the area. Kirk et al. (2005) did not find a correlation between the levels of perchlorate in breast milk and perchlorate in drinking water, but speculated that there was a correlation between higher levels of perchlorate and lower levels of iodine in breast milk. The objective of the Kirk et al. (2007) study was to determine the variability of perchlorate, thiocyanate, and iodide in breast milk in serially collected samples (6 samples on each of the 3 study days) involving 10 women. The authors concluded that “Iodine intake may be inadequate in a significant fraction of this study population. Perchlorate and thiocyanate



appear to be common in human milk. The role of these chemicals in reducing breast milk iodide is in need of further investigation.”

Blount et al. (2007) suggested breast milk as an excretion pathway and Dasgupta et al. (2008) compared a woman’s daily intake of iodine and perchlorate with the concentrations of each in her breast milk. The Dasgupta et al. study found that a higher proportion of perchlorate enters the breast milk compared with a small proportion of iodine.

Of those commenters that provided detailed comments to the October 2008 FR notice, many commenters believe that EPA’s RfD is not adequately protective of human health. One commenter stated that “[T]he EPA reference dose for perchlorate is based on data from Greer et al. (2002) that observed the inhibition of radioiodide uptake. Ginsberg and Rice (2005) identified several problems with the Greer et al. study that suggest the need for reevaluation of the value that serves as the foundation for regulatory decision-making,” and that, “. . . the results of the Blount study more closely reflect our understanding of the biological and toxicological processes pertaining to thyroid homeostasis, both in terms of thyroid hormone variability and the role of iodine.” The commenter “[S]trongly recommends that the CDC data analyzed in the study of Blount et al. (2006) and Blount et al. (2007) be used as the basis for the derivation of a new reference dose.”

Other commenters agree, stating that the use of the Greer et al. (2002) study “. . . is based on a limited clinical study of short duration and small sample size not representative of the variability in the human population,” and the “[U]se of these limited data to calculate a regulatory trigger level has been widely criticized as inadequate . . . and no longer reflects the best available data.”

Another commenter believes that “[A]dditional important data on pregnant women and their offspring have become available since the time of development of the EPA RfD in 2005 which would necessitate a reconsideration of the existing value . . . in addition EPA has discussed other data relevant to deriving an updated RfD in this Federal Register notice including Amitai et al., 2007, Blount et al., 2006, and studies discussing PBPK models.”

One commenter concludes by stating, “. . . [T]hat EPA has based its argument for not regulating perchlorate contamination in public water systems on a literature that is both limited and ill focused. We believe that EPA has not performed a sufficiently “thorough review” of the literature, that it has omitted important information, and that it has failed to perform its due diligence in the interpretation and analysis of the information that it did present. To correct this, EPA must employ the CDC study (Blount et al, 2006a) as the point of departure for RfD determination, and must focus on the neonate and infant as the most sensitive population.”

One commenter does not believe that additional analysis is warranted and that EPA should issue a final determination as soon as possible,” stating that “EPA has an extraordinary wealth of comprehensive, authoritative scientific information relating to perchlorate’s health effects, supplemented by extensive occurrence and exposure data. The Agency is therefore exceptionally well-positioned to issue a well-considered regulatory determination.” The commenter continues by stating,

. . . EPA has ample scientific and technical data to make a final determination on or before the planned date of December 2008. . . . [P]erchlorate is one of the most well-studied chemicals with detailed information on the mechanism of action, dose-response, and health effects. This issue also is not new. EPA released its first draft risk assessment on perchlorate in 1998, followed by a second in 2002. The 2005 NAS

report was a comprehensive review of the science. The animal and human studies that have been published since the NAS report reduce the uncertainty and reinforce the NAS panel's finding that there will not be any adverse health effects from perchlorate at environmentally-relevant concentrations.

New studies published since the NAS report increase the weight of evidence that the current RfD protects human health including the most sensitive members of our population. In addition, testimony by Congressional members and witnesses alike have discussed the lengthy amount of time that EPA has spent studying the health effects, urging the agency to issue a determination as soon as practicable. We join them in urging EPA to issue the final determination promptly.

An additional key scientific issue was raised by EPA's OIG in the report released for public comment "OIG Scientific Analysis of Perchlorate (External Review Draft)" (EPA. 2008g). The report states,

The OIG Analysis concludes that a single chemical risk assessment of perchlorate is not sufficient to assess and characterize the combined human health risk from all four NIS stressors, (i.e., thiocyanate, nitrate, perchlorate and lack of iodide) and that . . . Only a cumulative risk assessment can fully characterize the nature and sources of risk affecting this public health issue. Furthermore, a cumulative risk assessment allows an informed environmental decision to be made on how to mitigate the risk effectively.

The report goes on to say,

Potentially lowering the perchlorate drinking water limit from 24.5 ppb to 6 ppb does not provide a meaningful opportunity to lower the public's risk. By contrast, addressing moderate and mild iodide deficiency occurring in about 29% of the U.S. pregnant and

nursing population appears to be the most effective approach of increasing TIU [total iodide uptake] to healthy levels during pregnancy and nursing, thereby reducing the frequency and severity of permanent mental deficits in children.

The draft report, and comments submitted by EPA's Office of Water and Office of Research and Development, can be found in the Docket to this notice.

EPA agrees that additional important data have become available since the RfD was derived in 2005. However, EPA has evaluated the new data and has decided to make the regulatory determination based upon the current RfD. EPA will continue to evaluate any new perchlorate data to determine its relevance to the regulatory determination in accordance with the SDWA.

## **V. Next Steps**

The Agency will consider the information and comments submitted in response to this supplemental notice, as well as comments received on the October 10, 2008, FR notice, and all peer review comments before issuing a final regulatory determination for perchlorate and intends to do so as expeditiously as possible. EPA believes that the alternative analyses presented in this notice could lead the Agency to make a determination to regulate perchlorate.

## **VI. References**

- Amitai Y, Winston G, Sack J, Wasser J, Lewis M, Blount BC, Valentin-Blasini L, Fisher N, Israeli A, and Leventhal A. (2007). Gestational exposure to high perchlorate concentrations in drinking water and neonatal thyroxine levels. *Thyroid*. 17(9): 843-850.
- Blount, B.C., J.L. Pirkle, J.D. Osterloh, L. Valentin-Blasini, and K.L. Caldwell. 2006. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environmental Health Perspectives*. Vol. 114, No. 12. pp. 1865–1871.
- Blount, B.C., L. Valentin-Blasini, J.D. Osterloh, J.P. Mauldin, and J.L. Pirkle. 2007. Perchlorate Exposure of the US Population, 2001–2002. *J. Exposure Sci. Environ. Epidemiol* (2007) 17, 400-407.
- Dasgupta, P.K., A.B. Kirk, J.V. Dyke, and S.I. Ohira. 2008. Intake of Iodine and Perchlorate Excretion in Human Milk. *Environ. Sci. Technol.* Advance online publication accessed September 18, 2008.
- DeWoskin R. and C. Thompson. 2008. Renal clearance parameters for PBPK model analysis of early lifestage differences in the disposition of environmental toxicants. [Regul Toxicol Pharmacol](#). 2008 Jun;51(1):66-86.
- Ginsberg G, Rice D, 2005. *The NAS Perchlorate Review: Questions Remain about the Perchlorate RfD*. *Environ Health Perspectives* 113(9):1117-1119.
- Greer, M.A., G. Goodman, R.C. Pleuss, and S.E. Greer. 2002. Health effect assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodide uptake in humans. *Environ Health Perspect* Vol. 110. pp. 927–937.
- Kahn, H.D., and K. Stralka. 2008. Estimated daily average per capita water ingestion by child and adult age categories based on USDA's 1994-1996 and 1998 continuing survey of food

- intakes by individuals. *Journal of Exposure Science and Environmental Epidemiology* (2009) 19(4):396-404.
- Kirk, A.B., P.K. Martinelango, K. Tian, A. Dutta, E.E. Smith, and P.K. Dasgupta. 2005. Perchlorate and iodide in dairy and breast milk. *Environmental Science and Technology*. Vol. 39, No. 7. pp. 2011–2017.
- Kirk, A.B., J.V. Dyke, C.F. Martin, and P.K. Dasgupta. 2007. Temporal patterns in perchlorate, thiocyanate and iodide excretion in human milk. *Environ Health Perspect* Online Vol. 115, No. 2. pp. 182–186.
- Life Sciences Research Office, Federation of American Societies for Experimental Biology Prepared for the Interagency Board for Nutrition Monitoring and Related Research. 1995. Third Report on Nutrition Monitoring in the United States: Volume 1. U.S. Government Printing Office, Washington D.C.
- Murray, C.W III, S.K. Egan, H. Kim, N. Beru, P.M. Bolger. 2008. US Food and Drug Administration's Total Diet Study: Dietary Intake of Perchlorate and Iodine. *Journal of Exposure Science and Environmental Epidemiology*, advance online publication January 2, 2008.
- National Research Council (NRC). 2005. *Health Implications of Perchlorate Ingestion*. National Academies Press, Board on Environmental Studies and Toxicology. January 2005. 276 p.
- Pearce, E.N., A.M. Leung, B.C. Blount, H.R. Bazrafshan, X. He, S. Pino, L. Valentin-Blasini, L.E. Braverman. 2007. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. *J Clin Endocrin Metab* Vol. 92, No. 5, pp. 1673-1677

- Schier, J.G., A.F. Wolkin, L.Valentin-Blasini, M.G. Belson, S.M. Kieszak, C.S. Rubin, B.C. Blount. Journal of Exposure Science and Environmental Epidemiology advance online publication 18 March 2009; doi: 10.1038/jes.2009.18.
- Steinmaus, C., M.D. Miller, R. Howd. 2007. Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001-2002 National Health and Nutrition Examination Survey. Environ Health Perspect 115(9):1333-8.
- USEPA. 1995. Guidance for Risk Characterization. Science Policy Council, February, 1995.
- USEPA. 2004. Estimated Per Capita Water Ingestion and Body Weight in the United States - An Update. Office of Science and Technology, Washington, DC; EPA/822/R-00-001.
- USEPA. 2005. Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. National Center for Environmental Assessment, Washington, DC; EPA/630/P-03/003F.
- USEPA. 2008a. Drinking Water: Preliminary Regulatory Determination on Perchlorate, Federal Register, Vol. 73, No. 198. p. 60262, October 10, 2008.
- USEPA. 2008b. Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-Based Pharmacokinetic (PBPK) Modeling. Office of Research and Development, Washington, DC; EPA/600/R-08/106A.
- USEPA. 2008c. External letter peer review of EPA's draft report, Inhibition of the Sodium-Iodide Symporter by Perchlorate: An Evaluation of Lifestage Sensitivity Using Physiologically-based Pharmacokinetic (PBPK) Modeling. National Center for Environmental Assessment, Washington, DC; November 12, 2008.
- USEPA. 2008d. Interim Drinking Water Health Advisory for Perchlorate. Office of Science and Technology, Washington, DC; EPA 822-R-08-025.

USEPA. 2008e. Comment Response Summary Report, Peer Review of Drinking Water Health Advisory for Perchlorate. Office of Science and Technology, Washington, DC; December 2008.

USEPA. 2008f. Child-Specific Exposure Factors Handbook. National Center for Environmental Assessment, Washington, DC; EPA/600/R-06/096F.

USEPA. 2008g. Scientific Analysis of Perchlorate (External Review Draft). Office of Inspector General, Washington, DC; Assignment No. 2008-0010.

Dated:

Peter S. Silva

Assistant Administrator, Office of Water